REMARKS

Claims 4, 6, 8, 10, 12, 14-19, 22-26, 28 and 32-34 are pending in this application. Claims 15-19, 22-25, and 28 are withdrawn. Claim 4 is being amended. New claims 32-34 are presented. Claims 1-3, 5, 7, 9, 11, 13, 20-21, 27, and 29-31 are canceled.

The introduction of new claims 32-34 introduce no new subject matter. Support for the new claims may be found throughout the specification including, by way of example but not limitation, on page 3, lines 3-5, page 3, lines 28-31, page 5, lines 13-14, page 5, lines 28-30, and page 6, lines 12-15.

I. Maintained claim rejections under 35 U.S.C. § 112, first paragraph

The Examiner has maintained the rejection of claims 4, 6, 8, 10, 12, 14, and 26 under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement.

Applicants respectfully traverse the rejection and its supporting remarks. Regarding Applicant's argument 1, the Examiner alleges that the specification and claims do not place any limit on the number of amino acid substitutions, deletions, insertions, and/or deletions that may be made into the proteins listed. Applicants respectfully disagree and point out that the five claimed proteins are clearly limited by being capable of inducing a bactericidal antibody response. All five proteins have been described in detail in the instant specification or in references incorporated by reference. For example, references regarding immunological evaluations of different hybrids and of multiple variants of different antigens have been cited and incorporated by reference including those of the inventor of the current application (Ref. 14-16). By way of example, Ref. 16 (WO03/020756) includes data from testing five variants of GNA2132 against seven different meningococcal strains and found similar levels of immune response for each (see, e.g., page 20, lines 20-26 of WO03/020756). Thus, one skilled in the art generating a composition comprising the five meningococcal antigens capable of inducing bactericidal antibodies would certainly not generate random and irrelevant variants, especially since the instant specification provides guidance and references to each of the five antigens and hybrids thereof. Therefore, Applicants disagree with

the Examiner's argument that the practice of the composition of instant claim 4 would require that one of skill in the art generate of an almost infinite number of random polypeptides, since a Ph.D. scientist of ordinary skill would certainly not blindly generate any proteins but rather refer to the instant specification and the cited references listing the different versions of the antigens and hybrid variations taking into consideration the limitation that these antigens when combined need to be capable of inducing bactericidal antibodies against each of the hypervirulent lineages A4, ET-5 and lineage 3 of *N. meningitides* serogroup B.

The Examiner asserted that Applicant's argument 2 concerning *Falkner v. Inglis* would not provide any support of Applicant's position, because in *Falkner* the art taught what needed to be altered to achieve the claimed vaccine. The Applicant disagrees and respectfully asserts that Falkner provides support for Applicant's position. First, regarding *Falkner*, the Federal Circuit recognized that the earlier application mentioned in several places that the teachings of the invention could be applied to the creation of a poxvirus even though the disclosed embodiment was a herpesvirus. The court also noted that one of ordinary skill in the art would be able to use the lessons of the application regarding the herpesvirus to construct a similar poxvirus. The instant disclosure actually teaches the combination of five disclosed antigens of *N. meningitidis* serogroup B within the scope of the claims unlike in *Falkner*, and further refers to earlier applications (Re. 14-16) which include further details of the same five *N. meningitidis* serogroup B antigens and hybrids thereof (among a number of other antigens and hybrid combinations under consideration therein), , whereas in *Falkner* the Federal Circuit accepted the teaching of how to manipulate one virus (herpesvirus) combined with references relevant to the claimed virus (poxvirus) as enabling of the claimed virus (poxvirus). Second, the MPEP states (2100-172) that "as explained by the Federal Circuit, '(1) examples are not necessary to support the adequacy of a written description; (2) the written description standard may be met ... even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure.' Falkner v. Inglis, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006)." As discussed above, the instant disclosure provides an example regarding the combination of the five meningococcal

antigens that induces bactericidal antibodies, thus providing a reduction to practice. Furthermore, the amino acid sequences of all five antigens as shown in the working example have been disclosed. Numerous examples of these five antigens are referenced in the specification from other strains. Thus, one highly skilled in the art would recognize that the inventor was in possession of the scope of the claims as pending as only limited experimentation, if any, would be required to generate numerous variations of the five antigens capable of generating the claimed response based upon the guidance in the specification and the cited reference. A description of preferred forms of each antigen has also been included in the specification, so a scientist skilled in the art would be expected to understand how to generate the sequences commensurate with the scope of the claims and therefore recognize that the inventor had possession of such. The Examiner seems to imply that a Ph.D. level scientist would select random forms of the proteins and generate an unnecessary number of species, instead of using the preferred forms, with the disclosed working example being a successful result of these teachings. The Examiner further asserts that by fusion of proteins or altering the amino acid sequence the immune responses are altered and that the epitopes common across strains have not been described. Applicant notes that in Guiliani et al. (2006), the authors assumed that the altered immune response of NadA may have been due to the oligomeric structure of NadA being disrupted. By contrast, in cited Ref. 16 (WO03/020756), the inventor of the present application tested NadA (designated 961 therein) as hybrids with NMB1870 or NMB2091 and found both to provide protective immune responses against five or six meningococcal strains tested, respectively. The Examiner further requests that Applicant describes "a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus". As mentioned previously, the preferred forms of the five proteins and hybrids have been described in the specification. Furthermore as mentioned above, additional protein variants, including sequence information and experiments demonstrating the capability to induce bactericidal antibodies, have been cited to in the specification (Ref. 14-16). What this specification provides is a key piece of data that these five antigens and their variants work together to provide a broad protective immune response.

The Examiner further asserts that instant claim 4 recites laboratory designations that do not convey any structural or functional limitations, and which are not described in the specification.

Applicant respectfully traverses this rejection and accompanying remarks. The NMBxxxx designations based Tettelin et al (Science 2000; 287: 1809-1815) provide a clearly defined link to supplemental material available at Science Online (www.sciencemag.org/feature/data/1046515.shl.12) and to the corresponding sequences deposited in GenBank. The supplemental material lists genes of *N. meningitidis* serogroup B strain MC58 from the genome sequencing project using both the NMBxxxx nomenclature, as well as the common name of each gene. Applicant also notes that NadA (also referred to as NMB1994 in the specification), NMB1870, NMB2091, NMB1030, and NMB2132 genes and gene products, are listed in the supplemental materials and/or were deposited in GenBank at the time of publication with a reference to the Tettelin article. Moreover, a search of the GenBank (www.ncbi.nlm.nih.gov/sites/entrez) protein database using the NMBxxx nomenclature for NadA (NMB1994) reveals entries for NadA such as AAF42321 containing a 364 residue amino acid sequence. Thus one of skill in the art can readily recognize the metes and bounds of a claim that names an adhesion-specific protein using the NMBxxx nomenclature instead of a SEQ ID NO.

Applicant further notes that the sequence databases of the National Center for Biotechnology Information are well curated. Thus, while periodic updates of records occur, a complete revision history is maintained and accessible to the public via the "More Formats" pull down menu. Accordingly, comparing the original March 10, 2000, 3:54 pm version with the May 26, 2005, 8:11 am version using the revision history link of AAF42321 (corresponding to NMB1994 of Tettelin) and FASTA formatting indicates that the amino acid sequence of NMB1994 of these records are identical.

Additionally unauthorized changes to the GenBank sequence database are monitored and punishable by law as stated in the GenBank disclaimer (www.ncbi.nlm.nih.gov/About/disclaimer.html) under Conditions of Use.

> This site is maintained by the U.S. Government and is protected by various provisions of Title 18 of the U.S. Code. Violations of Title 18 are subject to criminal prosecution in a federal court. For site security purposes, as well as to ensure that this service remains available to all users, we use software programs to monitor traffic and to identify unauthorized attempts to upload or change information or otherwise cause damage. In the event of authorized law enforcement investigations and pursuant to any required legal process, information from these sources may be used to help identify an individual.

Thus, identification of an amino acid sequence using the NMBxxx nomenclature and the GenBank database is as definite and permanent a record as the use of a specific SEQ ID NO. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

II. New claim rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 4, 6, 8, 10, 12, 14, and 26 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprising the proteins with the sequences of NO:2, 7 and 8, does not reasonable provide enablement for the full breadth of the instant claims.

Applicants respectfully traverse the rejection and its supporting remarks. The Examiner discusses the Wands factors and asserts regarding the breadth of the claims, that the broadest claim encompasses an unlimited genus of any polypeptides capable of inducing the required immune response. Applicant disagrees, since the claim does not encompass an unlimited genus of any polypeptide. The broadest claim rather encompasses a composition of (1) meningococcal polypeptides, (2) comprising at least five antigens, (3) each antigen being recited by name: NadA, NMB2091, NMB1870, NMB1030, and NMB2132, (4) the combination of five antigens being capable to induce bactericidal antibodies against (5) hypervirulent lineages A4, ET-5 and lineage 3 of (6) *N. meningitides* serogroup B. Therefore, the genus is not unlimited, since all these five meningococcal antigens have in addition been clearly described of being capable to induce the desired immune response and preferred variants and hybrids have been referred to in the specification (Ref. 14-16). Moreover, an exemplary composition containing all five meningococcal proteins capable of inducing the desired bactericidal antibodies is included in the instant disclosure.

In conclusion, the Examiner's assertion of an unlimited genus of any polypeptides is clearly not justified, since it would imply that the broadest claim includes not only compositions of those five meningococcal antigens and variants with all characteristics as listed under (1) to (6) above, but would also include polypeptides of other origin such as viral, human or plant.

The Examiner further asserts that regarding Guidance of the specification/The existence of working examples, that the "specification does not disclose any other compositions (or variants of the above composition) that are capable of inducing the required bactericidal antibody response." The instant invention is related to a composition comprising the five defined meningococcal proteins NadA, NMB2091, NMB1870, NMB1030, and NMB2132 which together provide protection against defined hypervirulent lineages of serogroup B *N. meningitidis*. The provided working example demonstrates that the composition of these five proteins results into a composition with the required capabilities. The specification further discloses references (see paragraphs [0013], [0019], [0028], [0032], and [0036]) to these five antigens of instant claim 1. Exemplary variants are described and references are provided that evaluated these polypeptides for expression and for the capability to induce bactericidal antibodies. Moreover, preferred hybrids of two proteins, including the hybrids shown in the example of the instant working example, have been described (see References 14-16). As discussed above, in particular, Ref. 16 which was incorporated by reference and names the same inventors includes additional data regarding other variants and hybrid combinations which would assist one of skill in the art in the practice of the claimed invention. In conclusion, the specification in combination with the working example and the cited references has clearly provided sufficient guidance for a scientist skilled in the art to generate a realistic number of compositions commensurate with the scope of the claims.

The Examiner further asserts that the State of the art indicates that the skill in the art of immunology is high and that the prediction of a specific immune response is quite unpredictable. The Examiner continues and states that linear epitopes are generally not found on the surface of a protein and are only available to antibodies upon denaturation of a protein. Applicant disagrees with the Examiner since linear epitopes are well known in native proteins. Examples are the

neutralizing antibody to a linear V3 epitope of HIV-1 or a linear epitope on the fusion F protein of RSV against which a therapeutically active monoclonal antibody binds to (Palivizumab). Both proteins, gp120 of HIV-1 and F of RSV are surface proteins and as such clearly exposed, similar to the five meningococcal antigens used here for inducing bactericidal antibodies. More importantly, bactericidal antibodies directed to linear epitopes of serogroup B *N. meningitidis* have been reported, including against NBM1870 (SEQ ID:3) (Giuliani *et al*, 2005) and against linear outer membrane protein epitopes that are discussed by the authors to be potentially important in synthetic peptide or in recombinant protein vaccines containing linear bactericidal epitopes (Danelli et al., Current Microb, Vol. 31, 1995). Moreover, the Examiner further implies that "any change (including deletions and substitutions), anywhere along the polypeptide is likely to alter the three-dimensional structure and folding of the protein, thus altering the antibody-antigen interaction." However, Giuliani *et al.* revealed with a limited amount of experimentation the immunogenic regions of NMB1870 which allow substantial deletion of whole protein domains but still being able to induce bactericidal titers, comparable to the experiments shown in references 14-16 leading to the preferred proteins and hybrids to be used for the five protein composition as claimed in the instant disclosure. Thus, in view of the scientific knowledge discussed above and considering the preferred proteins disclosed in references 14-16 as indicated in the specification, there is no evidence for undue experimentation for a scientist skilled in the art to make and use the composition as claimed.

Applicants therefore respectfully request the withdrawal of the pending enablement rejection.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 223002100300. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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